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Title: Comparative effectiveness of metformin versus sulfonylurea on kidney function decline or death among patients with reduced kidney function: a retrospective cohort
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Reviewer 1
General comments (author response in bold)

The question of whether metformin still has any value in the era of SGLT2i and GLP-1RA has been controversial, with the European Society of Cardiology taking the firm position that SGLT2i and GLP1-RA should be started first in drug naïve individuals with end-organ indications; EASD/ADA and Diabetes Canada continue to support the use of metformin as first line antihyperglycemic therapy in adults with diabetes, though this is primarily based on “long-term experience with this agent” and “Grade D Consensus” in the Canadian guidelines.
We note that some guidelines are suggesting that newer agents should be used as first line medications. This topic is out of scope for this paper. In our opinion we believe that until SGLT2 and GLP1RA medications become as affordable as metformin the guidelines should continue to recommend metformin as first line therapy for diabetes treatment. Given the scope and scale of Type 2 diabetes throughout the US, advocating for a 500 dollar a month treatment rather than a 5 dollar a month treatment puts an unfair burden on patients and primary care doctors.

How the older randomized trial evidence showing macrovascular benefit of metformin should be valued compared to modern cardiovascular outcomes trials is part of this controversy. It is worth pointing out that the UKPDS trial (UKPDS-34) showing substantial macrovascular benefits metformin compared to sulfonylurea was underpowered to report on renal outcomes.
Noted and added to the introduction

Substantial evidence has accumulated demonstrating the safety of metformin from lactic acidosis concerns that initially inhibited its use in adults with CKD – now evidence from observational studies like this and from the lab-science literature is emerging suggesting benefit for CKD. This study therefore represents an important addition to a burgeoning field, which may have a role in changing the direction future clinical guidelines take on metformin therapy.
Noted

• The study is well-conducted.
Thank you

• The main limitation of generalizability / risk of selection bias with the selection on adults with eGFR <= 60 and persistent metformin / sulfonylurea monotherapy users is inevitable and appropriately referenced in the limitations. For a study that gets at an etiologic question, we can look past the selection effect. I do wonder whether the authors could comment on the contemporaneous factors that would have led drug naïve persons with diabetes to be started on sulfonylurea monotherapy vs metformin monotherapy during the study period. It could be made more clear that the cumulative incidence

results are limited to adults who did well enough long term to continue monotherapy long-term, and a broader population of adults may have a difference experience.
Noted and added to the limitations

• The supplement contains additional information that go a long way to making the methods clear. My only comment here is that the time period of the study and the fact that drug naieve adults were selected who had been initiated on monotherapy should be made explicit in the main manuscript.
Agreed and revised as above

• The explicit identification of competing risks and use of methods appropriate for competing risks is refreshing.
Thank you please see additional supplemental methods

• The results are both reasonable and interesting. The first-year data is mostly driven by lower mortality in metformin users and this matches well with much extant observational data showing the same thing. The second-year and onwards analysis has much more to say about kidney outcomes, and the report of a protective effect on a clinically-important renal outcomes is novel and important.
Thank you we will try to explain these strengths in the discussion.

• The interpretation is well supported by data in the results. I had no issues with the tables and figures, which are clear and transparent.
Thank you

• The results are well contextualized in the current literature. The results are highly relevant to any diabetes practitioner who prescribes metformin, and has had to grapple with whether metformin is worth “pushing” in the SGLT2i / GLP-1RA era.
Agreed

• The conclusions are pitched with a degree of certainty (using terminology “associated” and “provides reassurance”) for the study design.
Noted and changed to association throughout

• The manuscript is very well written, and I found the explication of a series of selection steps quite easy to follow.
Thank you. We hope that the manuscript is even clearer now